Nonlinear analysis of electroencephalogram and magnetoencephalogram recordings in patients with Alzheimer's disease

Non-linear analysis of EEG and MEG in patients with Alzheimer's disease

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The aim of the present study is to show the utility of non-linear methods to analyse the electroencephalogram (EEG) and magnetoencephalogram (MEG) in patients with Alzheimer's disease (AD). The following non-linear methods have been applied to study the EEG and MEG background activity in AD patients and control subjects: approximate entropy, sample entropy, multiscale entropy, auto-mutual information and Lempel-Ziv complexity. We discuss why these non-linear methods are appropriate to analyse EEG and MEG. Furthermore, the performance of all these methods has been compared when applied to the same databases of EEG and MEG recordings. Our results show that EEG and MEG background activities in AD patients are less complex and more regular than in healthy control subjects. In line with previous studies, our work suggests that non-linear analysis techniques could be useful in AD diagnosis.

Keywords: Alzheimer's disease, electroencephalogram, magnetoencephalogram, non-linear analysis

1. Introduction

The electromagnetic brain activity has been researched in the last decades by means of the electroencephalogram (EEG) and magnetoencephalogram (MEG). EEG records the electrical activity of the brain, whereas MEG is a measure of the magnetic brain activity. EEG and MEG are the only signals that record the synchronous oscillations of cortex pyramidal neurons directly and non-invasively. Both recordings reflect slightly different characteristics. EEG is sensitive to all primary currents while MEG is only affected by current flows oriented parallel to the scalp (Hämäläinen *et al.* 1993; Hari 2005). Other difference between EEG and MEG arises from the insensitivity of magnetic fields to inhomogeneities in the head. Electrical activity is more affected than magnetic oscillations by skull and extracerebral brain tissues. Moreover, EEG rhythms can be significantly influenced by some technical and methodological issues, like distance between electrodes, sensor placement or reference point. On the other hand, the magnetic fields emitted by the brain are extremely weak. Thus, MEG signals have to be detected using large arrays of SQUIDs (superconducting quantum interference devices) immersed in a cryogen, housed in a thermally insulated container. In addition, MEG instrumentation needs to be placed in a magnetically shielded room to reduce the environmental noise.

These issues increase the cost of MEG systems and reduce both their mobility and their availability (Hari 2005).

The theory of non-linear dynamics analysis (NDA) has provided new methods for the study of multi-variable complex systems. NDA has been widely applied in the last two decades to various physiological data to comprehend complex dynamics of the underlying processes (Jeong 2004; Stam 2005). The fundamental assumption of NDA is that EEG and MEG signals are generated by non-linear deterministic processes with non-linear coupling interactions between neuronal populations. Non-linearity in the brain is introduced even at the neuronal level (Andrzejak *et al.* 2001), since the dynamical behaviour of individual neurons is governed by threshold and saturation phenomena. Even though some cellular processes may be characterized by probability functions and the whole brain is continuously submitted to random external stimuli, there is evidence that neural systems may still exhibit non-linear behaviour (Abarbanel & Rabinovich 2001). Moreover, large networks of interconnected neurons are likely candidates for self-organized criticality, which refers to large systems with local non-linear interactions in which a slow build-up of some energy value is alternated with brief bursts of energy redistribution (Stam *et al.* 2005). Given this non-linear nature of the neuronal interactions at multiple levels of temporal and spatial scales, non-linear methods are appropriate to analyse EEG and MEG signals (Kantz & Schreiber 1997). The NDA application to the electromagnetic brain activity has opened up a range of new perspectives for the study of normal and disturbed brain function and is developing towards a new interdisciplinary field of non-linear brain dynamics (Stam 2005).

The first non-linear EEG studies were carried out by Rapp *et al.* (1985) and Babloyantz *et al.* (1985). Rapp *et al.* (1985) studied the spontaneous neural activity in the motor cortex of a monkey by means of a 'chaos analysis', while Babloyantz *et al.* (1985) published the first observations on the so called correlation dimension (D_2) of human sleep EEG. The early phase of non-linear EEG analysis was characterized by the search for low-dimensional chaotic dynamics in various types of EEG signals. However, some of the limitations of various algorithms derived from chaos theory for non-linear time series analysis became clear and the method of 'surrogate data testing' was introduced to check the validity of the results (Osborne & Provenzale 1989; Pijn *et al.* 1991; Theiler 1986; Theiler *et al.* 1992*a*,*b*). Subsequently, early claims for 'chaos' in the brain were critically re-examined and often rejected (Pritchard *et al.* 1995, Theiler & Rapp 1996). For this reason, non-linear EEG/MEG analysis has redirected its focus in two directions (Stam 2005): (i) the detection, characterization and modelling of non-linear dynamics rather than strict deterministic chaos; (ii) the development of new non-linear measures which are more suitable to be applied to noisy, non-stationary and high dimensional EEG/MEG data. Nevertheless, recent results provide converging evidence that non-linear EEG analysis allows one to reliably characterize different states of brain function and dysfunction, provided that limitations of the respective analysis techniques are taken into consideration and results are interpreted with care (Lehnertz *et al.* 2003).

There is growing evidence that non-linear techniques are extremely useful to characterize the brain activity in several pathological states, such as epilepsy and psychiatric disorders or different dementias (Stam 2005). These investigations of the electromagnetic activity of the brain have revealed possible medical applications, since NDA yields information unavailable from traditional spectral-band analysis

(Czigler *et al.* 2008; Pritchard *et al.* 1994). Non-linear time series analysis techniques have been applied to different kinds of EEG from humans, such as recordings from healthy volunteers at rest (Stam *et al.* 1999), during periods of cognitive activity (Theiler & Rapp 1996) or to study changes in non-linear dynamics with maturation and aging (Anokhin *et al.* 1996). Moreover, there are non-linear EEG studies in patients with Parkinson's disease (Pezard *et al.* 2001), epilepsy (Andrzejak *et al.* 2006; Feucht *et al.* 1999; Hornero *et al.* 1999; Lehnertz *et al.* 2001, 2003; Möller *et al.* 1998), depression (Nandrino *et al.* 1994) or schizophrenia (Fell *et al.* 1995) in comparison with control subjects. Recently, there is an increased interest to study abnormal brain dynamics in Alzheimer's disease (AD) (Stam 2005), which is the most common neurodegenerative disease.

Due to the increase in life expectancy, AD is a neurological disorder of particular relevance. AD is a primary degenerative dementia of unknown aetiology that gradually destroys brain cells and represents the most prevalent form of dementia in western countries (Bird 2001; Nestor *et al.* 2004). AD is characterized by progressive impairments in cognition and memory whose course lasts several years prior to the patient's death (Jeong 2004). Structural changes in AD are related to the accumulation of amyloid plaques between nerve cells in the brain and with the appearance of neurofibrillary tangles inside them (Jeong 2004). The clinical diagnosis of AD is made primarily on the basis of medical history studies, psychiatric evaluation and different memory, reasoning and mental status tests. Nevertheless, the diagnostic accuracy values in AD are under 90% and a definite diagnosis is only possible by necropsy (Rossor 2001). Thus, new approaches are necessary to improve AD diagnosis.

Several studies have examined the EEG background activity in AD patients with non-linear methods, particularly with D_2. It has been found that AD patients have lower D_2 values than control subjects (Jeong *et al.* 1998, 2001*a*; Stam *et al.* 1995). These results show a decrease in the complexity of the electrical activity in brains injured by AD (Jeong 2004). Furthermore, Besthorn *et al.* (1995) showed that a lower D_2 was correlated with increased severity of dementia and suggested that this reduced D_2 may be associated with an increase in the proportion of lower-frequency component in the AD patients' EEGs. Pritchard *et al.* (1994) reported that the addition of non-linear measures (D_2) and a neural net classification procedure to linear methods improved the classification accuracy of AD patients and controls up to 92%. Additionally, coherence and a global D_2 measure were computed from EEG data filtered in several frequency bands. The results showed that both measures, when computed in comparable ways, are related metrics which can assess the decreased functional cortical connectivity of AD (Jelles *et al.* 2008). Moreover, Jeong *et al.* (1998, 2001*a*) found that AD patients have significantly lower values of the largest Lyapunov exponent ($L1$) than age-matched controls, reflecting a drop in the flexibility of information processing in the injured brain (Jeong 2004).

However, the theoretical limitations of D_2 and $L1$ make necessary to study the EEG background activity with other non-linear techniques suitable to be applied to noisy, non-stationary and high-dimensional data. Non-linear forecasting and entropy maps have been used to characterize drug effects on brain dynamics in AD (Pezard *et al.* 1998). Information transmission between different cortical areas in AD has been characterized with mutual information (MI) (Jeong *et al.* 2001*b*) and synchronization likelihood (Stam *et al.* 2003*b*, 2005). This kind of non-linear syn-

chronization measure may complement traditional spectral power metrics in the detection of AD (Czigler *et al.* 2008). Recent entropy-based studies have shown that the EEG background activity is more regular in AD patients than in control subjects (Abásolo *et al.* 2005, 2006*a*). Moreover, some studies have also confirmed the decrease of EEG complexity in AD with suitable non-linear techniques like Lempel-Ziv (*LZ*) complexity (Abásolo *et al.* 2006*b*) or multiscale entropy (*MSE*) (Escudero *et al.* 2006).

D_2 has also been used to examine the hypothesis that AD is associated with a decrease in the complexity of MEG activity (van Cappellen van Walsum *et al.* 2003). Additionally, the results of D_2 were compared to those obtained with a neural complexity measure (C_N) in several frequency bands. AD patients' D_2 values were significantly lower in delta and theta bands and significantly higher in beta. Furthermore, contrary to the initial hypothesis of C_N, the variations reflected by this parameter were opposite of those shown by D_2 (van Cappellen van Walsum *et al.* 2003). Another complexity measure, the *LZ* complexity, has also been applied to MEG signals in AD (Gómez *et al.* 2006). This study also found that demented patients' MEG background activity is less complex than in control subjects (Gómez *et al.* 2006). Entropy-related statistics have shown that this decrease in complexity is accompanied by an increase in regularity in AD patients' MEGs (Gómez *et al.* 2007, Hornero *et al.* 2008). Furthermore, it has been observed that spectral and non-linear analyses from MEG spontaneous activity could be complementary methods to help in AD detection (Hornero *et al.* 2008). Finally, synchronization measures have also been used to assess the information transmission in AD patients' MEG activity (Stam *et al.* 2002, 2006).

In addition to non-linear studies, other approaches have also been used to improve AD diagnosis, such as spectral measures applied to electromagnetic brain recordings, laboratory studies, neuroimaging techniques and molecular genetic analyses. Spectral analysis has associated AD with an increased EEG/MEG activity in lower frequency bands. Babiloni *et al.* (2004) found that the EEG in AD is characterized by a mean power increase in delta and theta frequency bands, and a decrease in alpha and beta bands. Other study showed increased slower and reduced faster activity in AD patients' MEGs (Fernández *et al.* 2006). Laboratory studies, as thyroid-function tests and measurement of the serum vitamin B12 level, are necessary to identify secondary causes of dementia and coexisting disorders that are common in elderly people (Blennow *et al.* 2006). Additionally, neuroimaging techniques are particularly helpful in excluding alternative causes of dementia (Cummings 2004). For instance, Scheltens *et al.* (1992) showed a reduction in medial temporal lobe and hippocampal volume of AD patients as compared to controls using magnetic resonance imaging. Finally, genetic analyses suggest that mutations in the genes presenilin 1 (chromosome 14), presenilin 2 (chromosome 1) and amyloid precursor protein (chromosome 21) increase the risk of suffering from AD (Borchelt *et al.* 1996).

The major aim of this article is to describe and explain the utility of some non-linear methods in the analysis of the electromagnetic brain activity in AD and to compare its performance. Firstly, the non-linear methods are introduced in section 2. The results obtained from EEG and MEG analyses to help in AD diagnosis with these non-linear techniques are presented in section 3. Finally, in section 4, the relevant results are discussed and the conclusions are drawn.

2. Methods

Today it is commonly accepted that the existence of a chaotic or even a non-linear deterministic structure underlying neuronal dynamics is difficult, if not impossible, to prove (Lehnertz *et al.* 2003). Some of the non-linear techniques most frequently used to characterize the EEG and MEG background activity in AD are D_2 and $L1$. D_2 reflects the number of independent variables that are necessary to describe the system dynamics (Jeong 2004). This measure is based on the correlation integral, C_ρ, which represents the likelihood that any two randomly chosen points on the signal attractor will be closer than a given distance ρ. The correlation integral is computed for a range of ρ values. Then, if the embedding dimension is high enough, the slope of a linear scaling region of $\log(C_\rho)/\log(\rho)$ is an estimate of D_2 (Stam 2005). While D_2 is a static, geometric measure, $L1$ is a relatively dynamic metric that can be interpreted as a flexibility measure of information processing in the brain (Fell *et al.* 1995; Jeong 2004). $L1$ summarizes the divergence of trajectories starting at close initial states (Jeong 2004). It is based upon measuring the exponential increase or decrease over time of the inter-vector distances for nearby points in the signal attractor (Stam 2005). Despite the widespread use of D_2 and $L1$ to characterize electromagnetic brain activity, it is important to note that these measures present some drawbacks: (i) they require an amount of data to obtain meaningful results that is beyond the experimental possibilities for physiological data (Eckmann & Ruelle 1992) and (ii) assume the time series to be stationary (Grassberger & Procaccia 1983), a criterion hard to satisfy with biological data. Thus, there is room for improvement of the current studies using new non-linear measures suitable to be applied to noisy, non-stationary and high dimensional EEG/MEG data. In this section, we introduce some non-linear metrics that fulfil these conditions and overcome the limitations of the classical methods derived from chaos theory.

(*a*) *Approximate Entropy (ApEn)*

ApEn is a family of statistics introduced to quantify the regularity of a sequence (Pincus 2001). It assigns a non-negative number to a time series, with larger values corresponding to more irregularity in the data. A run length m and a tolerance window r must be specified to compute *ApEn* (Pincus 2001). Briefly, given N points, $ApEn(m, r, N)$ measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on subsequent incremental comparisons.

Given N data points from a time series $\{x(n)\} = x(1), x(2), \ldots, x(N)$, one should follow these steps to compute *ApEn* (Pincus 2001):

1. Form $N - m + 1$ vectors $X(1), X(2), \ldots, X(N - m + 1)$ defined by: $X(i) = [x(i), x(i+1), \ldots, x(i+m-1)]$, $i = 1, \ldots, N-m+1$. These vectors represent m consecutive x values, commencing with the ith point.

2. Define the distance between $X(i)$ and $X(j)$, $d[X(i), X(j)]$, as the maximum norm:

$$d[X(i), X(j)] = \max_{k=1,\ldots,m}(|x(i + k - 1) - x(j + k - 1)|) \tag{2.1}$$

3. For a given $X(i)$, count the number of j ($j = 1, \ldots, N-m+1$) so that $d[X(i), X(j)] \leq r$, denoted as $N^m(i)$. Then, for $i = 1, \ldots, N-m+1$,

$$C_r^m(i) = \frac{N^m(i)}{N-m+1} \tag{2.2}$$

$C_r^m(i)$ measures, within a tolerance r, the frequency of patterns similar to a given one of window length m.

4. Compute the natural logarithm of each $C_r^m(i)$, and average it over i,

$$\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_r^m(i) \tag{2.3}$$

5. Increase the dimension to $m+1$. Repeat steps 1 to 4 and find $C_r^{m+1}(i)$ and $\phi^{m+1}(r)$.

6. We define *ApEn* by:

$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \tag{2.4}$$

(b) Sample Entropy (SampEn)

The *ApEn* algorithm counts each sequence as matching itself to avoid the occurrence of ln(0) in the calculations and this has led to discussion of the bias of *ApEn* (Richman & Moorman 2000). *SampEn* was introduced to reduce this bias (Richman & Moorman 2000). Two input parameters, a run length m and a tolerance window r, must be specified to compute *SampEn*. *SampEn*(m, r, N) is the negative logarithm of the conditional probability that two sequences similar for m points remain similar at the next point, where self-matches are not included in calculating the probability. Thus, a lower value of *SampEn* also indicates more self-similarity in the time series. *SampEn* is largely independent of record length and displays relative consistency under circumstances where *ApEn* does not (Richman & Moorman 2000). In addition to eliminating self-matches, the *SampEn* algorithm is simpler than the *ApEn* algorithm.

Formally, given N data points from a time series $\{x(n)\} = x(1), x(2), \ldots, x(N)$, to define *SampEn*, one should follow these steps (Richman & Moorman 2000):

1. Form m-vectors $X_m(1), X_m(2), \ldots, X_m(N-m+1)$ following the procedure defined in the first step of the algorithm for the computation of *ApEn*. The distance between $X_m(i)$ and $X_m(j)$ is defined as in equation (2.1).

2. For a given $X_m(i)$, count the number of j ($1 \leq j \leq N-m, j \neq i$), denoted as B_i, such that the distance between $X_m(i)$ and $X_m(j)$ is less than or equal to r. Then, for $1 \leq i \leq N-m$,

$$B_i^m(r) = \frac{1}{N-m-1} B_i \tag{2.5}$$

3. Define $B^m(r)$ as:

$$B^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r) \tag{2.6}$$

4. We increase the dimension to $m+1$ and calculate A_i as the number of $X_{m+1}(i)$ within r of $X_{m+1}(j)$, where j ranges from 1 to $N-m$ ($j \neq i$). We then define $A_i^m(r)$ as:
$$A_i^m(r) = \frac{1}{N-m-1} A_i \tag{2.7}$$

5. We set $A^m(r)$ as:
$$A^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r) \tag{2.8}$$
Thus, $B^m(r)$ is the probability that two sequences will match for m points, whereas $A^m(r)$ is the probability that two sequences will match for $m+1$ points.

6. We define *SampEn* by:
$$SampEn(m, r, N) = -\ln \left[\frac{A^m(r)}{B^m(r)} \right] \tag{2.9}$$

It is imperative to consider $ApEn(m, r, N)$ and $SampEn(m, r, N)$ as families of parameters: comparisons are intended with fixed m, r and N. N is the length of the time series, m is the length of the sequences to be compared and r is the tolerance for accepting matches. It is convenient to set the tolerance as r times the standard deviation (SD) of the original data sequence. This gives *ApEn* and *SampEn* scale invariance, in that they remain unchanged under uniform process magnification, reduction, or constant shift to higher or lower values (Pincus 1991; Richman & Moorman 2000).

Although m and r are critical in determining the outcome of *ApEn* and *SampEn*, no guidelines exist for optimizing their values. In principle, the accuracy and confidence of the entropy estimate improve as the number of matches of length m and $m+1$ increases. The number of matches can be increased by choosing small m (short templates) and large r (wide tolerance) (Lake *et al.* 2002). However, there are penalties for criteria that are too relaxed (Pincus 1991). For smaller r values, one usually achieves poor conditional probability estimates, while for larger r values, too much detailed system information is lost.

(*c*) *Multiscale Entropy (MSE)*

MSE is a new complexity measure that focuses on determining the information expressed by the signals on multiple time scales (Costa *et al.* 2005). It is based on the idea that physiologic systems are regulated by interacting mechanisms that operate across multiple spatial and temporal scales (Costa *et al.* 2005). This complexity measure incorporates the interrelationship of entropy and scale and fulfils the requirement of vanishing for absolutely random or regular systems (Costa *et al.* 2002). The *MSE* analysis is based on calculating the *SampEn* of several coarse-grained sequences, which represent the system dynamics on different time scales, ϵ (Costa *et al.* 2005). Then, the *MSE* curves are constructed by plotting the *SampEn* values as a function of ϵ. These curves allow us to relatively compare the complexity of the analysed time series (Costa *et al.* 2005). To build the coarse-grained time

series corresponding to the scale factor ϵ, $\left\{y^{(\epsilon)}(j)\right\}$, we divide the original time series into non-overlapping windows of length ϵ, and then we average the values of the data points inside each window:

$$y^{(\epsilon)}(j) = \frac{1}{\epsilon} \sum_{i=(j-1)\epsilon+1}^{j\epsilon} x(i), 1 \leq j \leq \left\lfloor \frac{N}{\epsilon} \right\rfloor \tag{2.10}$$

Once those coarse-grained time series are built, we calculate their *SampEn*.

(*d*) *Auto-mutual information (AMI)*

MI provides a measure of both the linear and non-linear statistical dependencies between two time series (Jeong *et al.* 2001*b*). The *MI* between two measurements taken from a single time series $x(n)$ separated by time delay τ estimates, on average, the degree to which $x(n+\tau)$ can be predicted from $x(n)$. In this paper, this measure will be denotated by *AMI*. The *AMI* betwen $x(n)$ and $x(n+\tau)$ is (Jeong *et al.* 2001*b*):

$$AMI(\tau) = \sum_{k,l} P_{kl}\left[x(n), x(n+\tau)\right] \cdot \log_2 \left\{ \frac{P_{kl}\left[x(n), x(n+\tau)\right]}{P_k\left[x(n)\right] \cdot P_l\left[x(n+\tau)\right]} \right\} \tag{2.11}$$

where $P_k\left[x(n)\right]$ and $P_l\left[x(n+\tau)\right]$ are the probability density functions estimated using the histograms of the values observed for $x(n)$ and $x(n+\tau)$, respectively, and $P_{kl}\left[x(n), x(n+\tau)\right]$ is the estimated joint probability density for the measurements of $x(n)$ and $x(n+\tau)$.

As the *AMI* is correlated with entropy, the decrease rate of *AMI* with increasing time delays can be used to characterize time series (Jeong *et al.* 2001*b*).

(*e*) *Lempel-Ziv (LZ) complexity*

To estimate the *LZ* complexity, the signal $\{x(n)\}$ must be transformed into a finite symbol sequence, typically a binary one (Lempel & Ziv 1976). By comparison with a threshold T_d, the original signal samples are converted into a 0-1 sequence $\{s(n)\} = s(1), s(2), \ldots, s(N)$, with $s(i)$ defined by: $s(i) = 0$ if $x(i) < T_d$ and $s(i) = 1$ if $x(i) \geq T_d$. We used the median as T_d due to its well-known robustness to outliers.

The sequence $\{s(n)\}$ is then scanned from left to right and the complexity counter $c(N)$ is increased by one unit every time a new subsequence of consecutive characters is encountered (Zhang *et al.* 2001). In order to obtain a complexity measure which is independent of the sequence length, $c(N)$ should be normalized (Zhang *et al.* 2001). In general, $N/\log_\alpha(N)$ is the upper bound of $c(N)$, where the base of the logarithm α is the number of symbols (2 for a binary sequence). Thus,

$$\lim_{N\to\infty} c(N) = b(N) \equiv \frac{N}{\log_\alpha(N)} \tag{2.12}$$

where $\equiv$ denotes identity and $c(N)$ can be normalized via $b(N)$:

$$C(N) = \frac{c(N)}{b(N)} \tag{2.13}$$

$C(N)$, the normalized LZ complexity, reflects the arising rate of new patterns along with the sequence, capturing its temporal structure. Larger values correspond to more complexity (Zhang *et al.* 2001).

3. Results

(*a*) *Non-linear EEG analysis in AD*

Twenty-two subjects participated in this study: 11 patients (5 men and 6 women; age = 72.5 ± 8.3 years; mean ± SD) fulfilling the criteria of probable AD and 11 elderly control subjects without past or present neurological disorders (7 men and 4 women; age = 72.8 ± 6.1 years; mean ± SD). The Mini-mental state examination (MMSE) score for the AD patients was 13.1 ± 5.9 (mean ± SD) whereas all control subjects had an MMSE equal to 30. The difference in the mean age of both populations was not statistically significant ($p = 0.9313$, Student's t-test). A more detailed description of the database, the EEG recording procedure and the pre-processing step prior to the non-linear analysis can be found elsewhere (Abásolo *et al.* 2006*a*).

The non-linear metrics were estimated for channels F3, F4, F7, F8, Fp1, Fp2, T3, T4, T5, T6, C3, C4, P3, P4, O1 and O2. Results were averaged based on all the artefact-free 5 s (1280 samples) epochs within the 5 minute period of EEG recordings. The Kolmogorov-Smirnov and the Levene's tests were used to assess normality of distribution and homocedasticity, respectively. After this exploratory analysis, variables met parametric test assumptions. Student's t-test was used to evaluate the statistical differences between the values of the non-linear metrics for AD patients and control subjects. The Bonferroni correction was applied to the p-values to avoid spurious positives. Differences between groups were considered significant if $p < 0.05$. Furthermore, the ability to discriminate AD patients from control subjects at the electrodes where $p < 0.05$ was evaluated using Receiver Operating Characteristic (ROC) curves (Zweig & Campbell 1993). A ROC curve is a graphical representation of the trade-offs between sensitivity and specificity. We define sensitivity as the rate of AD patients who test positive, whereas specificity represents the fraction of controls correctly recognized. Accuracy quantifies the total number of subjects precisely classified.

ApEn and *SampEn* were estimated with $m = 1$ and $r = 0.25$ times the SD of the original data sequence, as they provide good statistical reproducibility for sequences longer than 60 samples, as considered herein (Pincus 2001). Both *ApEn* and *SampEn* values were lower in AD patients than in control subjects at 15 electrodes, with significant differences between groups ($p < 0.05$) at P3, P4 and O1. These results suggest that AD patients' EEG activity is more regular than in a normal brain (Abásolo *et al.* 2006*a*).

The *MSE* was estimated with $m = 1$, $r = 0.25$ times the SD of the original time series and a maximum time scale $\epsilon_{MAX} = 12$. Hence, the shortest coarse-grained sequence built has more than 100 points. Our selection of m and r is able to produce good statistical reproducibility for time series with this number of samples or larger, as the coarse-grained sequences we are considering (Lake *et al.* 2002). The *MSE* profiles representing the *SampEn* values of each coarse-grained sequence versus the scale showed two distinct slopes (Escudero *et al.* 2006). For small time scales ($1 \leq \epsilon \leq 5$), the *MSE* profiles were characterized by a steep slope

while the slope was much smoother on large time scales ($6 \leq \epsilon \leq 12$). Whereas the irregularity of the coarse-grained time series decreased on the larger time scales in the control group, the coarse-grained sequences of the AD patients were usually slightly more irregular as we analysed larger time scales. *SampEn* values were higher in controls than in AD patients for most time scales, suggesting that the former have a more complex EEG background activity than the latter (Costa *et al.* 2005). No significant differences between both groups were found ($p > 0.05$) for the small time scales ($1 \leq \epsilon \leq 5$). On the other hand, the slope for large time scales ($6 \leq \epsilon \leq 12$) decreases at all electrodes for the control subjects, while AD patients have an increasing slope at most electrodes (Escudero *et al.* 2006). Significant differences between groups ($p < 0.05$) were found at electrodes Fp1, Fp2, T5, T6, P3, P4, O1 and O2.

The *AMI* of the EEG from AD patients and control subjects was calculated for time delays between 0 and 0.5 s. The normalized average *AMI* curves of the control subjects and AD patients decrease with increasing values of the time delay for all subjects at all electrodes. As the *AMI* rate of decrease can be used to characterize a time series (Jeong *et al.* 2001*b*), its value was estimated from time delay 0 to the first relative minimum value. Therefore, different time scales were simultaneously taken into account when inspecting the signal properties. With the exception of electrode T4, the *AMI* decreases more slowly in AD patients at all electrodes, with significant differences ($p < 0.05$) at T5, P3, P4 and O1. Furthermore, there is a strong correlation between *ApEn* or *SampEn* and the *AMI* rate of decrease, with Pearson's correlation coefficient lower than -0.90 for most electrodes ($p << 0.05$).

AD patients have significantly lower *LZ* complexity values ($p < 0.05$) at electrode P3, suggesting that the EEG activity of AD patients is less complex than in a normal brain at certain regions (Abásolo *et al.* 2006b).

Finally, we evaluated the ability of *ApEn*, *SampEn*, *AMI*, *MSE* and *LZ* complexity to discriminate AD patients from control subjects at the electrodes where significant differences were found using ROC plots. For each method, the optimal threshold was selected as the value at which the highest accuracy was obtained. Table 1 summarizes our results.

(*b*) *Non-linear MEG analysis in AD*

Twenty AD patients (7 men and 13 women; age = 73.05 ± 8.65 years, mean ± SD) fulfilling the criteria of probable AD and 21 elderly control subjects without past or present neurological disorders (9 men and 12 women; age = 70.29 ± 7.07 years, mean ± SD) participated in this study. The MMSE scores for the AD patients and the control subjects were 17.85 ± 3.91 and 29.10 ± 1.00 (mean ± SD), respectively. The difference in the mean age of both groups was not statistically significant ($p = 0.2613$, Student's t-test). A complete description of the populations, MEG recording procedure and pre-processing applied to the MEG signals can be found in Gómez *et al.* (2007).

ApEn, *AMI* and *LZ* complexity were applied to 20 s (3392 samples) artefact-free epochs of MEG background activity. The results of each non-linear analysis method were averaged within the 5 minutes MEG recording to obtain one value per channel and subject. Likewise the EEG case, the Kolmogorov-Smirnov test was used to verify normality of distribution, whereas homocedasticity was evaluated

Table 1. *Test results for the non-linear techniques on the channels in which the differences between both groups' EEGs were significant.*

Method	Electrode	Sensitivity (%)	Specificity (%)	Accuracy (%)
ApEn	P3	72.73	81.82	77.27
	P4	63.64	81.82	72.73
	O1	81.82	72.73	77.27
SampEn	P3	72.73	81.82	77.27
	P4	63.64	90.91	77.27
	O1	81.82	72.73	77.27
MSE	Fp1	90.91	90.91	90.91
	Fp2	100	72.73	86.36
	T5	90.91	81.82	86.36
	T6	81.82	81.82	81.82
	P3	81.82	90.91	86.36
	P4	72.73	90.91	81.82
	O1	81.82	90.91	86.36
	O2	81.82	81.82	81.82
AMI	T5	90.91	72.73	81.82
	P3	100	81.82	90.91
	P4	81.82	81.82	81.82
	O1	81.82	81.82	81.82
LZ complexity	P3	72.73	90.91	81.82

with Levene's test. Since variables met parametric test assumptions, a Student's t-test with a Bonferroni correction was applied to assess whether there were statistically significant differences between groups. The significance level was set to 0.05. Additionally, a ROC analysis was used to evaluate the ability of each method to properly classify the subjects.

ApEn was computed with the commonly used parameter values of $m = 1$ and $r = 0.25$ times the SD of the analysed time series (Pincus 2001). *ApEn* values were lower in AD patients than in controls for all MEG channels. Differences between groups were statistically significant at 9 of the 148 channels ($p < 0.05$). These results suggest that the MEG background activity is more regular in AD patients than in elderly controls (Hornero *et al.* 2008).

The *AMI* of the MEG signals was estimated over a time delay from 0 to 0.5 s and it was normalised so that $AMI(\tau = 0) = 1$. Then, we estimated the slope of this profile from $\tau = 0$ to its first relative minimum value (Jeong *et al.* 2001*b*). The absolute values of the *AMI* rate of decrease were lower for AD patients than in control subjects. These differences were significant in 111 channels ($p < 0.05$). The smoother *AMI* rate of decrease found in the patient group indicates that this dementia produces a more predictable MEG background activity (Gómez *et al.* 2007).

The complexity of the MEG recordings was evaluated with *LZ* complexity (Lempel & Ziv 1976). We found that the *LZ* complexity values were lower for the AD patients, with significant differences at 144 channels ($p < 0.05$). Thus, these results lead us to think that the AD patients' MEG background activity shows abnormal

Table 2. *Test results for the non-linear analysis of the MEG recordings computed from the values averaged over the 148 channels.*

Method	Sensitivity (%)	Specificity (%)	Accuracy (%)
ApEn	75.0	66.7	70.7
AMI	75.0	90.5	82.9
LZ complexity	85.0	85.7	85.4

patterns characterized by a diminished complexity in Kolmogorov's sense (Gómez *et al.* 2006).

Finally, we assessed the ability of these non-linear methods to classify the subjects. Due to the high spatial density of the MEG channels, the dimensionality was reduced to simplify this analysis. The mean of the 148 values for each subject and non-linear method was computed (Gómez *et al.* 2007). Then, the ROC analysis was performed using only this mean value. For each non-linear method, the optimal threshold was selected as the value in which the highest accuracy was obtained. The results of this analysis are displayed in Table 2.

4. Discussion and conclusions

In this study, we have introduced results obtained in recent years with several non-linear methods that were applied to analyse the EEG and MEG background activity in AD patients. This dementia is of particular relevance due to the rise in life expectancy. NDA has provided tools that might help to better understand the brain activity and to complement results obtained with linear techniques.

Our work shows that non-linear techniques are particularly suitable to analyse the EEG background activity in AD patients. In particular, we found that *ApEn* and *SampEn* were significantly lower in the AD patients' EEG at P3, P4 and O1 ($p < 0.05$). Theoretically, *SampEn* is less dependent of the signal length and shows more consistency on a broader range of m, r and N values than *ApEn* (Richman & Moorman 2000). Nevertheless, the differences between *ApEn* and *SampEn* are subtle and thus the results found using both metrics were very similar. This implies that, despite the fact that *SampEn* has some theoretical advantages over *ApEn*, both methods provided similar outcomes when applied to our EEG database. Moreover, our results show that the *AMI* decreases more slowly with increasing time delays in AD patients. We have found significant differences between the *AMI* rates of decrease from both groups at electrodes T5, P3, P4 and O1 ($p < 0.05$). Furthermore, the absolute values of the *AMI* rate of decrease are strongly correlated with *ApEn* and *SampEn*. This strong correlation suggests that the *AMI* rate of decrease might be used to quantify the regularity of a time series. A complexity measure should vanish for both completely regular and completely random system (Costa *et al.* 2005), something that neither happens with *ApEn*, nor with *SampEn*. Although these metrics are strongly correlated, the *AMI* rate of decrease offers advantages over *SampEn* and *ApEn*. This is due to the fact that the *AMI* inspects different time scales simultaneously, something that might characterize the time series in a more adequate way.

Unlike the relatively simple *MSE* profile that characterizes random signals, the shape of the *MSE* profiles of the EEGs reveals their complex structure (Escudero

et al. 2006). As the *MSE* profile values are higher in control subjects than in AD patients for most scales, it can be concluded that EEG background activity is less complex in patients, something that is also in agreement with our *LZ* complexity results. Furthermore, the *MSE* profile slope for large time scales in AD patients is significantly different than in control subjects at 8 electrodes, while *LZ* complexity only reflected significant differences at 1 electrode. *LZ* complexity assesses the number of different substrings and the rate of their recurrence along the original time series (Lempel & Ziv 1976). In contrast, *MSE* is based on the idea that physiological systems are governed by interacting mechanisms that operate across multiple scales (Costa *et al.* 2005). To inspect these interactions, *MSE* uses the concepts of scale and entropy, as it applies the *SampEn* to analyse different coarse-grained versions of the original time series (Costa *et al.* 2005). Considering the results obtained with *MSE* and *LZ* complexity, it seems clear that analysing different time scales might provide a better insight into the EEG background activity characteristics and the changes associated with AD.

Our results with the aforementioned non-linear techniques suggest that the EEG background activity in AD patients is more regular and less complex than in control subjects and are in agreement with previous studies that have shown EEG changes in AD with non-linear techniques (Jeong *et al.* 1998*b*, 2001*a*,*b*; Stam *et al.* 1995). Our analysis shows that the most relevant differences appear at the electrodes located on the posterior region. Differences between AD patients and healthy control subjects at similar locations have been found by other authors using both spectral and non-linear analyses (Jeong 2002, 2004). Nevertheless, there are discrepancies between different studies which may be due to differences in patient populations (Jeong 2002). In any case, these alterations in the electromagnetic brain activity might be explained by the neuro-pathological changes induced by AD in temporal and parietal regions (Nestor *et al.* 2004; Rossini *et al.* 2007). Although a simple relation between an impaired electromagnetic brain activity and cognitive dysfunction does not exist (Stam *et al.* 2005), these abnormalities might influence the electromagnetic brain activity.

The results from the non-linear analysis of MEG recordings showed significant differences between AD patients and control subjects at most channels for the rate of decrease of the *AMI* and the *LZ* complexity, indicating an abnormal type of dynamics associated with AD. *ApEn* values and the absolute values of the *AMI* rate of decrease were lower in the AD group. Thus, it can be inferred that the electromagnetic background activity of brains affected by AD is more regular than in control subjects. Additionally, *LZ* complexity revealed that the MEG background activity of the AD patients was less complex than in elderly controls. This finding is in agreement with other research work that studied MEG activity in AD with D_2 (van Cappellen van Walsum *et al.* 2003).

It should be mentioned that we have been careful to select model-independent techniques well suited to the analysis of biomedical signals. All these techniques can be applied to relatively short, noisy and non-stationary time series, irrespective of whether their origin is stochastic or deterministic (Costa *et al.* 2005; Jeong *et al.* 2001*b*; Lempel & Ziv 1976; Pincus 2001; Richman & Moorman 2000). Thus, this set of measures is much better suited for EEG and MEG analysis than traditional non-linear techniques as $L1$ and D_2 from a signal processing point of view.

AD patients' brain recordings have been also analysed with linear techniques

based on coherence and spectral calculations. These analyses seem to discriminate AD patients from control subjects through an increased EEG/MEG activity in lower frequency bands associated with this dementia (Babiloni *et al.* 2004; Fernández *et al.* 2006). To be more precise, a decreased mean frequency, an increase in delta and theta power, and a decrease in alpha and beta power are observed in AD patients compared to that of normal elderly subjects (Babiloni *et al.* 2004; Fernández *et al.* 2006; Jeong 2004; Rossini *et al.* 2007). The earliest changes are an increase in theta activity and a decrease in beta activity, which are followed by a decrease in alpha activity, and then an increase in delta activity (Jeong 2004). Given the wide variety of linear and non-linear methods that may be adequate to analyse brain signals (Jeong 2004; Stam 2005), there is a strong need for comparative studies that aim at deciding which techniques are best suited to help in clinical diagnosis and to provide physiologically meaningful markers of the diverse neurological disorders. Hence, several authors have attempted to point out which methods are better suited to these tasks. Quian Quiroga *et al.* (2002) showed that both linear and non-linear synchronization measures are useful in EEG analysis and provide information no accessible by visual inspection. They also suggested that all the analysed measures may give similar results, although non-linear methods may provide a higher sensitivity than linear ones (Quian Quiroga *et al.* 2002). A similar conclusion was drawn by Jelles *et al.* (2008), who applied a linear (coherence) and a non-linear (global D_2) measure to AD patients' EEGs to assess the functional connectivity in several frequency bands. Additionally, Andrzejak *et al.* (2006) showed that surrogate-corrected non-linear measures performed better than linear and non-linear techniques when analysing intracranial EEG signals to detect the epileptic seizure-generating hemisphere. Nevertheless, Ansari-Asl *et al.* (2006) suggested that linear measures performed equally good or even better than non-linear ones. The main conclusion of these studies is that no method performs better than the others in all situations. In fact, previous studies of the electromagnetic brain activity in AD show that linear and non-linear methods could provide complementary information (Abásolo *et al.* 2005; Czigler *et al.* 2008; Hornero *et al.* 2008; Pritchard *et al.* 1994).

Our results lead us to conclude that the non-linear EEG/MEG analysis show significant differences between AD patients and healthy control subjects. Despite the fact that different subject groups were involved in the EEG and MEG studies, the results obtained from these two kinds of signals are in agreement (Abásolo *et al.* 2005, 2006*a*,*b*; Escudero *et al.* 2006; Gómez *et al.* 2006, 2007; Hornero *et al.* 2008). This consistency may be due to the fact that the primary currents generating the EEG and MEG activity are the same (Hari 2005). Nevertheless, it should be noted that some methodological issues related to the EEG, such as the reference point and the conductive of the body tissues, might affect the non-linear analyses of the electromagnetic brain activity (Stam *et al.* 2003*a*). On the other hand, due to the extremely low amplitude of brain magnetic fields, the cost of MEG equipment is higher than that of EEG (Hari 2005). In both signals, better classification accuracies were reached using the *AMI* rate of decrease and the *LZ* complexity than with *ApEn*. Nevertheless, these results should be taken with caution due to the small sample sizes and to the different approaches adopted in the subject classification. Whereas in the EEG case an electrode-based classification was computed, the results of the non-linear analyses carried out on MEG signals were averaged over

all channels to reduce the dimensionality. This implies a loss of spatial information, which could reduce the classification accuracy. This problem may be partially avoided by computing the average of every parameter for a number of brain regions. However, in that case, it should be considered that a MEG recording channel does not necessarily measure only the brain oscillations under that sensor, but it can reflect activity from other areas.

The increased regularity and decreased complexity in the AD patients' EEG and MEG could be explained by a decrease of dynamical complexity of part of the brain. Several authors have suggested diverse mechanisms that can be responsible for these alterations in the electromagnetic brain dynamics. An animal model has indicated that acetylcholine loss produces a decrease of high-frequency and an increase of slow-frequency couplings (Villa *et al.* 2000). Considering this finding, it may be hypothesized that the abnormalities found in EEG and MEG dynamics result from anatomical disconnections among different cortical regions, which are essential for interactions between brain regions (Jelles *et al.* 2008), or reduced cholinergic coupling interactions between cortical neurons (Jeong 2004). Thus, the decrease in dynamical complexity could be due to neuronal death, a general effect of neurotransmitter deficiency or connectivity loss of local neural networks (Jeong 2004). If the decrease in dynamical complexity found in EEG and MEG channels is interpreted as a reduction of the degrees of freedom, it might be an expression of strongly coupled oscillators, a loss of dynamical brain responsivity to stimuli or the inactivation of previously active networks or neurons (Jeong 2002; Jeong *et al.* 1998). This interpretation based on inactivation of groups of neurons could also be derived from the conceptual model recently introduced by Stam (2005) to interpret the results from NDA of EEG and MEG activity. In this model, functional sources at a low resolution level are functional networks at a higher resolution level (Stam 2005). In our case, we can view the functional sources recorded at the EEG and MEG channels as a functional network formed by groups of neurons. Then, it can be hypothesized that the decrease in dynamical complexity related to AD is caused by loss of neurons (i.e. the neural network is partially inactivated, thus losing degrees of freedom). Nevertheless, any interpretation of these changes in terms of the synchronization level should be taken with caution, as it has been suggested that coupling measures applied at the functional network level are more reliable synchronization estimators than measures applied at the functional source level (Stam 2005).

Although our results indicate that non-linear techniques could be useful in AD diagnosis, some limitations must be considered and addressed in future studies. Firstly, the sample size in our studies was small. To prove the usefulness of these techniques as an AD diagnostic tool, this approach should be extended on a much larger patient population. Moreover, the detected regularity increase and loss of complexity in the EEG and MEG is not specific to AD and further work must be carried out to examine non-linear brain electromagnetic activity in other types of pathologies, as vascular dementia (Jeong *et al.* 2001*a*), schizophrenia (Na *et al.* 2001) and epilepsy (Jing & Takigawa 2000). In particular, it will also be interesting to thoroughly compare our results with those obtained with other non-linear entropies like, for instance, the permutation entropy (Bandt & Pompe 2002) or the corrected conditional entropy (Porta *et al.* 1998) and with those derived from spectral methods. Moreover, the changes produced by AD within individual frequency

bands should be studied with these and other analysis methods, as some non-linear studies have shown that not all frequency bands are equally affected by AD (Czigler *et al.* 2008; Jelles *et al.* 2008; van Cappellen van Walsum *et al.* 2003). Even with these considerations in mind, our work suggests that non-linear analysis techniques could be useful in AD diagnosis and complementary to traditional linear techniques that are widely used in clinical sciences.

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